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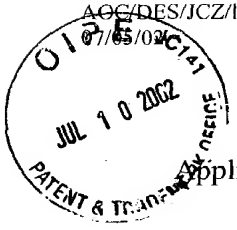
PATENT APPLICATION
Attorney's Docket No.: 0975.1005-012



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Junming Le, Jan Vilcek, Peter Daddona, John Ghrayeb, David M. Knight and Scott Siegel		
Application No.:	09/897,724	Group:	1642
Filed:	July 2, 2001	Examiner:	Not Assigned

For: ANTI-TNF ANTIBODIES AND PEPTIDES OF HUMAN TUMOR NECROSIS FACTOR

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to Assistant Commissioner for Patents, P.O Box 2327, Arlington, VA 22202

on July 5, 2002 (Date) Linda M. Amato (Signature)

Linda M. Amato
Typed or printed name of person signing certificate

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
P.O. Box 2327
Arlington, VA 22202

Sir:

This Preliminary Amendment is being filed in response to the Notice to File Missing Parts of Application mailed from the U.S. Patent and Trademark Office on January 4, 2002 in the above-identified application. Reconsideration and further examination are requested.

Please amend the application as follows:

In the Specification

Substitute drawings (Figures 1-33H) in compliance with 37 C.F.R. §1.84 are being submitted herewith.

Please replace the paragraph at page 1, line 27 through page 2, line 5 with the following paragraph:

Cells other than monocytes or macrophages also make TNFα. For example, human non-monocytic tumor cell lines produce TNF (Rubin, et al., *J. Exp. Med.* 164:1350 (1986); Spriggs, *et al.*, *Proc. Natl. Acad. Sci. USA 84*:6563 (1987)). CD4+ and CD8+ peripheral blood T lymphocytes and some cultured T and B cell lines (Cuturi, *et al.*, *J. Exp. Med. 165*:1581 (1987); Sung, *et al.*, *J. Exp. Med. 168*:1539 (1988)) also produce TNFα.

Amendments to the specification are indicated in the attached "Marked Up Version of Amendments" (page i).

In the Claims

Please cancel Claims 1-18.

Please add new Claims 19-56 as follows.

19. (New) A method of treating a TNF-mediated blood pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF antibody competitively inhibits binding of TNF to monoclonal antibody cA2.

20. (New) A method of treating a TNF-mediated blood pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody cA2, or a TNF binding fragment thereof.

21. (New) A method of treating a TNF-mediated blood pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF decapeptide pins which overlap at every second amino acid.

22. (New) A method of treating a TNF-mediated blood pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF dodecapeptide pins which overlap at every second amino acid.

23. (New) A method of treating a TNF-mediated blood pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody does not bind to one or more epitopes included in amino acids 11-13, 37-42, 49-57 or 155-157 of SEQ ID NO: 1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF decapeptide pins which overlap at every second amino acid.

24. (New) A method of treating a TNF-mediated blood pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody comprises a non-human variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:5.

25. (New) The method of Claim 24, wherein the non-human variable region is murine.

26. (New) The method of Claim 24, wherein the non-human variable region comprises a polypeptide encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4.

27. (New) The method of Claim 19, wherein the TNF-mediated blood pathology is associated with Crohn's Disease.

28. (New) The method of Claim 19, wherein the TNF-mediated blood pathology is associated with rheumatoid arthritis.

29. (New) The method of Claim 19, wherein the TNF-mediated blood pathology is leukopenia.

30. (New) The method of Claim 19, wherein the anti-TNF chimeric antibody is administered to the human by means of parenteral administration.

31. (New) The method of Claim 19, wherein the anti-TNF chimeric antibody is administered to the human by means of intravenous administration, subcutaneous administration, or intramuscular administration.

32. (New) The method of Claim 19, wherein the anti-TNF chimeric antibody is administered orally.

33. (New) The method of Claim 19 further comprising administering to the human an effective amount of a therapeutic agent selected from the group consisting of: disease-modifying anti-rheumatic drugs, anti-inflammatory agents, anti-neoplastic agents, radionuclides, radiotherapeutics, immunosuppressives, cytotoxic drugs, monoclonal antibodies, murine antibodies, chimeric antibodies, antibody fragments, antibody regions, lymphokines, cytokines, hemopoietic growth factors and immunoglobulins.

34. (New) The method of Claim 33, wherein the therapeutic agent is a disease-modifying anti-rheumatic drug.

35. (New) The method of Claim 34, wherein the disease-modifying anti-rheumatic drug is selected from the group consisting of: auranofin, azathioprine, chloroquine, D-penicillamine, gold sodium thiomalate hydroxychloroquine, Myocrisin and sulfasalzine methotrexate.

36. (New) The method of Claim 33, wherein the therapeutic agent is an anti-inflammatory agent.

37. (New) The method of Claim 36, wherein the anti-inflammatory agent is selected from the group consisting of: pentasa, mesalazine, asacol, codeine phosphate, benorylate, fenbufen, naprosyn, diclofenac, etodolac and indomethacin, aspirin and ibuprofen.

38. (New) The method of Claim 33, wherein the therapeutic agent is an anti-neoplastic agent.

39. (New) The method of Claim 38, wherein the anti-neoplastic agent is selected from the group consisting of: daunorubicin, doxorubicin, Mitomycin C and cyclophosphamide.

40. (New) The method of Claim 33, wherein the therapeutic agent is a pain control agent.

41. (New) The method of Claim 40, wherein the pain control agent is selected from the group consisting of: paracetamol and dextropropoxyphene.

42. (New) The method of Claim 19 further comprising administering to the human an effective amount of at least one therapeutic agent selected from the group consisting of: at least one antibiotic and at least one steroid.

43. (New) The method of Claim 19, wherein the anti-TNF chimeric antibody is of immunoglobulin class IgG1, IgG2, IgG3, IgG4, or IgM.

44. (New) The method of Claim 19, wherein the anti-TNF chimeric antibody is a fragment selected from the group consisting of Fab, Fab', $F(ab')_2$ and Fv.

45. (New) A method of treating a TNF-mediated blood pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric

antibody, wherein said anti-TNF chimeric antibody comprises an IgG1 constant region and competitively inhibits binding of TNF to monoclonal antibody cA2.

46. (New) A method of treating a TNF-mediated blood pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody comprises an IgG1 constant region and binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF decapeptide pins which overlap at every second amino acid.

47. (New) A method of treating a TNF-mediated blood pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody comprises an IgG1 constant region and binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF dodecapeptide pins which overlap at every second amino acid.

48. (New) A method of treating a TNF-mediated blood pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody comprises an IgG1 constant region and does not bind to one or more epitopes included in amino acids 11-13, 37-42, 49-57 or 155-157 of SEQ ID NO: 1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF decapeptide pins which overlap at every second amino acid.

49. (New) A method of treating a TNF-mediated blood pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody comprises an IgG1 constant region and does not bind to one or more epitopes included in amino acids 11-13, 37-42, 49-57 or 155-157 of SEQ ID NO: 1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF dodecapeptide pins which overlap at every second amino acid.

50. (New) A method of treating a TNF-mediated blood pathology in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody comprises a non-human variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:5 and an IgG1 human constant region.

51. (New) The method of Claim 50, wherein the non-human variable region is murine.

52. (New) The method of Claim 50, wherein the non-human variable region comprises a polypeptide encoded by a nucleic acid sequence selected from the group consisting of SEQ ID NO:2 and SEQ ID NO:4.

53. (New) A method of treating a human with hemoglobin levels below normal comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF antibody competitively inhibits binding of TNF to monoclonal antibody cA2.

54. (New) A method of treating a TNF-mediated blood pathology in a human comprising administering to the human a single or divided 0.1 - 100 mg/kg dose of an anti-TNF chimeric antibody, wherein said anti-TNF antibody competitively inhibits binding of TNF to monoclonal antibody cA2.

55. (New) A method of treating a TNF-mediated blood pathology in a human comprising administering to the human a single or divided 0.1 - 100 mg/kg dose of an anti-TNF chimeric antibody, wherein said anti-TNF antibody competitively inhibits binding of TNF to monoclonal antibody cA2, and wherein the single or divided dose of anti-TNF chimeric antibody is selected from the group consisting of: a 0.1 - 1 mg/kg dose, a 1.0 - 5 mg/kg dose, a 5 - 10 mg/kg dose and a 10 - 20 mg/kg dose.

56. (New) An anti-idiotypic antibody, or functional fragment thereof, that binds specifically to a chimeric or humanized antibody that binds to human TNF-α.

REMARKS

The specification was objected to on the grounds that it did not comply with 37 C.F.R. §1.52, specifically the line spacing in the specification, claims or abstract was not 1-1/2 or double spaced. Only originally filed Claims 1-18 were single spaced and were, therefore, not in compliance with 37 C.F.R. §1.52. However, since Claims 1-18 are cancelled in this amendment and replaced with new Claims 19-56, which are properly spaced and in compliance with 37 C.F.R. §1.52. Reconsideration and withdrawal of the objection is respectfully requested.

An amendment to the Specification is necessary to correct an inadvertent typographical error, specifically the last sentence of the first page was truncated. Support for this amendment can be found on page 1, lines 35-36 of U.S. Application Serial No. 08/192,093, filed February 4, 1994, to which priority is claimed under 35 U.S.C. 120. The application is entirely incorporated in the present specification by reference (09/897,724 specification, page 1, lines 11-12)

Substitute Figures 1-33H in compliance with 37 C.F.R. §1.84 is being submitted herewith. Two photographs, original Figures 16 and 32, as filed, have been deleted. The original photographs were unavailable and are not necessary for an understanding of the invention.

New Claims 19-52, 54 and 55 are directed to methods of treating a TNF-mediated blood pathology comprising administering an anti-TNF chimeric antibody in humans. Support for new Claims 19-55 can be found throughout the specification, for example, at page 61, lines 15-31.

The antibody in Claims 19 and 45 competitively inhibits the binding of TNF to monoclonal antibody cA2. The antibody of Claim 20 is cA2, or a TNF binding fragment thereof. The antibody of Claims 21 and 46 binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF decapeptide pins which overlap at every second amino acid. The antibody of Claims 22 and 47 binds to at least one epitope included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO:1 of hTNF, as determined by Gysen epitope

mapping comprising use of TNF dodecapeptide pins which overlap at every second amino acid. The antibody of Claims 23 and 48 does not bind to one or more epitopes included in amino acids 11-13, 37-42, 49-57 or 155-157 of SEQ ID NO: 1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF decapeptide pins which overlap at every second amino acid. The antibody of Claim 49 does not bind to one or more epitopes included in amino acids 11-13, 37-42, 49-57 or 155-157 of SEQ ID NO: 1 of hTNF, as determined by Gysen epitope mapping comprising use of TNF dodecapeptide pins which overlap at every second amino acid. Further support for Claims 19-23 and Claims 45-49 can be found, for example, at page 20, lines 11-25 and page 92, lines 15-36.

The antibody of Claims 24-26 comprises a non-human variable region comprising an amino acid sequence selected from the group consisting of SEQ ID NO:3 and SEQ ID NO:5. Further support for Claims 24-26 and Claims 50-52 can be found, for example, at page 10, lines 13-24, at page 12, lines 19-24, and at page 18, lines 16-25.

The TNF-mediated blood pathology is associated with Crohn's disease, rheumatoid arthritis and leukopenia, respectively. Further support for Claims 27-29 can be found, for example, at page 61, line 22 to page 63, line 29, and page 103, lines 34-36.

Claims 30-32 are directed to specific routes of administration. Further support for Claims 30-32 can be found, for example, at page 64, lines 5-8.

Claims 33-42 are directed to methods furthers comprising administering to a human an effective amount of a therapeutic agent. Further support for Claims 33-42 can be found, for example, in Table 12, pages 119-121, at page 2, lines 14-22, page 41, lines 20-31, and page 64, lines 10-16.

Claims 43 and 44 recite specific immunoglobulins and fragments thereof. Further support for Claims 43 and 44, can be found, for example, at page 27, lines 6-27, page 33, lines 5-11, and page 36, lines 12-29.

The antibody of Claims 45-52 comprise an IgG1 constant region. Further support for Claims 45-52, can be found, for example, at page 27, lines 6-27, page 33, lines 5-11, and page 36, lines 12-29.

Claim 53 is directed to a method of treating a human with hemoglobin levels below normal comprising administering to the human an effective TNF-inhibiting amount of an anti-

TNF chimeric antibody, wherein said anti-TNF antibody competitively inhibits binding of TNF to monoclonal antibody cA2. Further support for Claim 53 can be found, for example, at page 116, lines 26-27 and Table 14, at pages 122-123.

Claims 54 and 55 are directed to administering a single or divided dose of anti-TNF chimeric antibody. Further support for Claims 54-55 can be found, for example, at page 64, line 28 to page 65, line 5.

New Claim 56 is the same as Claim 1 as originally filed. Claim 1 has been cancelled and added as Claim 56 to revise the line spacing of the claim. No new matter has been added.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned at (978) 341-0036.

Respectfully submitted,

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09/897,724

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MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Replace the paragraph at page 1, line 27 through page 2, line 5 with the below paragraph marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

Cells other than monocytes or macrophages also make TNFα. For example, human non-monocytic tumor cell lines produce TNF (Rubin, et al., *J. Exp. Med.* 164:1350 (1986); Spriggs, *et al.*, *Proc. Natl. Acad. Sci. USA 84*:6563 (1987)). $CD4^+$ and $CD8^+$ peripheral blood T lymphocytes and some cultured T and B cell lines (Cuturi, *et al.*, *J. Exp. Med. 165*:1581 (1987); Sung, *et al.*, *J. Exp. Med. 168*:1539 (1988)) also produce TNFα.